TITLE PAGE

Statistical Analysis Plan

A Phase 1 Dose Escalation and Cohort Expansion Study of TSR-033, an anti-LAG-3 Monoclonal Antibody, alone and in combination with an anti-PD-1 in Patients with Advanced Solid Tumors

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Phase:	Phase 1
Methodology:	Open-Label, Single-Arm
Sponsor:	GlaxoSmithKline (Formerly Tesaro, Inc)
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SPONSOR SIGNATURE PAGE

Protocol Title:	A Phase 1 Dose Escalation and Cohort Expansion Study of TSR-033, an anti-LAG-3 Monoclonal Antibody, alone and in combination with an anti-PD-1 in Patients with Advanced Solid Tumors
Protocol Number:	213349 (4040-01-001)
Sponsor:	GlaxoSmithKline
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	Collegeville, PA, 19426

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance and guidelines.

Author:

PPD

Signature:

Associate Statistician,

Date:

GlaxoSmithKline

Approver:

PPD

Signature:

PPD

Date:

GlaxoSmithKline

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LIST OF ABBRIVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE(s)	adverse event(s)
BMI	body mass index
BOR	best overall response
CI	confidence interval
CR	complete response
CRC	colorectal cancer
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end-of-treatment
FDA	Food and Drug Administration
FUP	follow-up
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NE	not evaluable
ORR	objective response rate
OS	overall survival
PD	progressive disease

Abbreviation	Definition
PD-1	programmed cell death-1 receptor
PD-L1	programmed death ligand-1
PD-L2	programmed death ligand-2
PDv	Protocol deviation
PDy	pharmacodynamic
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PT	preferred term
Q2W	every 2 weeks
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event
TIL	tumor-infiltrating lymphocytes
TIM-3	T-cell immunoglobulin and mucin containing protein-3
ULN	upper limit of normal

1 INFORMATION FROM THE STUDY PROTOCOL

1.1 Introduction and Objectives

1.1.1 Introduction

The recognition of tumors by the immune system has been appreciated for multiple decades and has provided an impetus to utilize the immune system to control tumor growth. Studies have reported the presence of tumor-infiltrating lymphocytes (TILs) as a positive prognostic feature in multiple tumors, supporting a role for the immune system in limiting tumor growth. Despite evidence of immune reactivity, tumors are able to grow in the presence of an immune system, suggesting a suboptimal innate immune response.

Emerging research into this inadequate immune response has identified an important family of proteins that play key roles in immune checkpoint pathways, regulatory cascades that ordinarily maintain immune homeostasis, but are co-opted by cancer cells so that they may evade detection and subsequent destruction by the immune system. Prominent proteins within this immune checkpoint family include programmed cell death receptor (PD-1), associated with immune system downregulation and self-tolerance, and lymphocyte activation gene-3 (LAG-3) which is widely associated with exhausted or dysfunctional T cells that show varying degrees of functional impairment in the context of chronic antigen exposure.

To date, PD-1 has been a popular development target of anti-cancer therapies. However, despite favorable response rates observed with these therapies, there remains a large number of patients who derive little clinical benefit from this treatment approach (primary resistance) or suffer a relapse post-treatment (acquired or adaptive immune resistance). To potentially engender a stronger and more durable anti-tumor response, it is thought that a combined treatment approach that targets both PD-1 and LAG-3, complementary immune pathways in intrinsic tumor-cell resistance, may be successful. This belief is bolstered by internal results in the mixed lymphocyte reaction (MLR) assay and efficacy in syngeneic tumor models, which, taken together, provide a rationale for combination therapy with anti-PD-1 and anti-LAG-3 antibodies in cancer.

Two such therapeutic antibodies that target PD-1 and LAG-3 are dostarlimab and TSR-033, respectively. Dostarlimab is a potent humanized immunoglobulin G4 (IgG4) κ monoclonal antibody (mAb) that binds to PD-1 and blocks the interaction between PD-1 and its ligands, programmed cell death ligand-1 (PD-L1) and programmed cell death ligand-2 (PD-L2). The functional antagonist activity of dostarlimab was confirmed in a MLR assay demonstrating enhanced interleukin-2 (IL-2) production upon addition of dostarlimab. Dostarlimab is being studied as monotherapy and in combination in several tumor types to evaluate its safety and tolerability, pharmacokinetics (PK), pharmacodynamics (PDy), and clinical activity in participants with advanced or metastatic solid tumors. TSR-033 is a potent and selective humanized IgG4κ mAb that

will undergo dose-limiting studies and safety and tolerability assessment in participants with advanced or metastatic solid tumors, both alone and in combination with dostarlimab, in Part 1 of this study.

Colorectal cancer (CRC) is one of the most common malignancies worldwide and remains a deadly disease (second most common cause of cancer death in the United States [US]) despite current therapeutic options, which include the current standard of care (SOC), chemotherapy with or without anti-angiogenic antibodies or anti-epidermal growth factor receptor (EGFR) antibodies as first- and second-line regimens. In the US, although the incidence rate of CRC in adults aged ⩾50 years has declined in recent decades, it has increased by 13% in those aged <50 years. In addition, if the disease progresses to become metastatic CRC (mCRC), it is usually incurable. While colorectal cancers with microsatellite instability are frequently sensitive to check point inhibitor therapy, they make up only about 3% of patients with metastatic disease. Unfortunately, in contrast to many other areas of cancer therapy, the advances achieved with immunotherapy have not yet been replicated in the remaining 97% of patients whose mCRC is microsatellite stable CRC (MSS-CRC). Therefore, MSS-CRC remains an area of great and urgent medical need.

Among the cytotoxic chemotherapy choices for CRC, oxaliplatin- and irinotecan-based chemotherapy regimens are most commonly utilized, with clinical outcomes improved by the addition of biologics targeting EGFR or vascular endothelial growth factor (VEGF) or its receptor (VEGFR) in appropriate patients4. With regard to oxaliplatin-based regimens, FOLFOX and its variants (ie, modified FOLFOX6 [mFOLFOX6], FOLFOX4) remain popular and are used globally. FOLFOX consists of folinic acid (FOL) or leucovorin, 5-fluorouracil (F), and oxaliplatin (OX). mFOLFOX6, given with or without bevacizumab (anti-VEGF mAb), is by far the most commonly used regimen, clinically and in studies, for first-line therapy in CRC. An alternative 3-drug combination is FOLFIRI, which consists of irinotecan (IRI) in addition to FOL and F.This combination can also be given with biologics. While it is generally considered that FOLFOX and FOLFIRI are equivalent regimens, particularly with regard to overall survival (OS), the oxaliplatin-based regimens are utilized more frequently than irinotecan-based regimens in the first-line metastatic setting globally. In the second-line metastatic setting, a number of contemporary trials have established reliable benchmarks for overall response rates and progression-free survival (PFS), as well as OS, with FOLFOX- or FOLFIRI-based regimens. Taken together, the overall response rate with FOLFOX or FOLFIRI chemotherapy with or without biologics appears to be modest in CRC, in the 4% to 15% range.

Beyond second-line therapy, TAS-102, an oral fluoropyrimidine analogue and thymidine phosphorylase inhibitor, has demonstrated an improvement of OS by 1.8 months in participants with refractory disease versus best supportive care (5.3 versus 7.1 months [HR 0.68, 95% CI 0.58 to 0.81; p<0.001]). In addition, two anti-EGFR monoclonal antibodies, cetuximab and panitumumab, have shown efficacy as monotherapy in the

third-line setting in participants with KRAS wild type tumors. Monotherapy with the anti-angiogenic drug regorafenib has also yielded a modest survival benefit of 1.4 months (6.4 versus 5.0 months [HR ratio 0.77; 95% CI 0.64 to 0.94; one-sided p=0.0052). Finally, immunotherapy with checkpoint inhibitors as monotherapy appears to be active only in patients with microsatellite instability–high (MSI-H) or mismatch repair–deficient (dMMR) CRC. Both nivolumab and pembrolizumab are currently approved for MSI-H or dMMR CRC that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan. In summary, the current treatment options in first- through fourth-line CRC, their response rates, and the growing knowledge around subtypes of CRC patients, highlight the need for more efficacious therapeutics and support the decision to study TSR-033 and dostarlimab combination therapy in MSS-CRC.

The purpose of Part 2A of the study is to assess the safety and initial efficacy of the combination of TSR-033 and dostarlimab in third- or fourth-line MSS-CRC. Part 2B will assess the safety profile and initial efficacy of mFOLFOX6 (Cohort B1) or FOLFIRI (Cohort B2) plus bevacizumab in combination with TSR-033 and dostarlimab in participants with second-line MSS-CRC who have progressed on a prior first-line regimen.

1.1.2 Study Objectives

The primary objectives of this study are as follows:

Part 1: Dose Escalation Cohorts (1a, 1b, and 1c):

- To define the recommended Phase 2 dose (RP2D) and schedule of TSR-033 as monotherapy (1a, 1b) and in combination with dostarlimab (1c).
- To evaluate the safety and tolerability (eg, number of patients experiencing DLTs, AEs/serious adverse events [SAEs]/irAEs, and abnormal hematology/clinical chemistry results) of TSR-033 as monotherapy (1a, 1b) and in combination with dostarlimab (1c) in patients with advanced or metastatic solid tumors

Part 2A: CRC Dose Expansion Cohort A*:*

- To evaluate the anti-tumor activity of TSR-033 in combination with dostarlimab in anti-PD(L)-1 naïve patients with advanced or metastatic MSS-CRC who have progressed following 2 or 3 prior lines of therapy as measured by objective response rate (ORR) assessed by the Investigators using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Part 2B: CRC Dose Expansion Cohorts B1 and B2:

- B1:
  To evaluate the safety and tolerability (eg, number of patients experiencing DLTs, AEs/SAEs/irAEs, and abnormal hematology/clinical chemistry results) of TSR-

033 and dostarlimab in combination added to mFOLFOX6 and bevacizumab in anti-PD-1-naïve patients with advanced or metastatic MSS-CRC following progression on frontline treatment with FOLFIRI (or variant), with or without biologics.

- B2:

To evaluate the safety and tolerability (eg, number of patients experiencing DLTs, AEs/SAEs/irAEs, and abnormal hematology/clinical chemistry results) of TSR-033 and dostarlimab in combination added to FOLFIRI and bevacizumab in anti-PD-1-naïve patients with advanced or metastatic MSS-CRC following progression on frontline treatment with FOLFOX (or variant), with or without biologics.

The secondary objectives (in Part 1 and Part 2, unless otherwise specified) of the study are as follows:

- To characterize the PK (eg, serum concentrations for Part 1 and Part 2 and derived PK parameters for Part 1, as data permit) and immunogenicity of TSR-033 alone, TSR-033 and dostarlimab in combination, and TSR-033 and dostarlimab in combination with chemotherapy and bevacizumab.
- To evaluate additional measures of clinical benefit, including
  - ORR by RECIST v1.1 (Part 1 and Part 2B)
  - Duration of response (DOR) by RECIST v1.1 (Part 2)
  - Disease control rate (DCR) by RECIST v1.1 (Part 2)

- B1:

To evaluate the anti-tumor activity of TSR-033 and dostarlimab added to mFOLFOX6 and bevacizumab in patients with advanced or metastatic MSS-CRC following progression on frontline treatment with FOLFIRI, with or without biologics, measured by the ORR as assessed by the investigator using RECIST v1.1.

- B2:

To evaluate the anti-tumor activity of TSR-033 and dostarlimab added to FOLFIRI and bevacizumab in patients with advanced or metastatic MSS-CRC following progression on frontline treatment with FOLFOX (or variant), with or without biologics, measured by the ORR as assessed by the investigator using RECIST v1.1.

1.1.3 Scope and Revision History

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analyses of study data in order to answer the study objectives. Participant populations to be used for analyses, data handling rules, statistical methods, and formats for data presentation are identified and provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

The SAP will outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

The SAP is a living document that will be created during the trial conduct. It will be maintained throughout the lifecycle of the trial. A working SAP (version 1.0) will be finalized to start programming activities. Important changes following approval of SAP v1.0 will be tracked in this section. A final version of the SAP will be signed off prior to the final database lock. Any changes to the methods described in the plan will be described and justified in the final CSR.

All PK data will be summarized descriptively and displayed in the listings associated with this SAP.

Table 1 Revision History

SAP version	Protocol version	eCRF version	Changes from previous version
1.0	6.0	16 April 2020	N/A

1.2 Study Design

1.2.1 Synopsis of Study Design

This is a multi-center, open-label, first-in-human, Phase 1 study evaluating the anti-LAG-3 antibody TSR-033 1) alone, 2) in combination with the anti-PD1 antibody dostarlimab, and 3) the combination of TSR-033 and dostarlimab with mFOLFOX6 or FOLFIRI and bevacizumab. The study will be conducted in 2 parts, with Part 1 consisting of dose escalation to determine the RP2D of TSR-033 as a single agent (Part 1a) and in combination with dostarlimab (Part 1c). RP2D decisions will be based on the occurrence of DLTs or PK[redacted] data, as available. Part 1b of the study will aim to better characterize the PK profile of TSR-033 [redacted]. These additional participants will not be considered evaluable for dose escalation purposes (ie, not included into the DLT-evaluable population) but will contribute to the overall safety assessment at the dose level being evaluated. In Part 2, these regimens will be evaluated in participants with advanced or metastatic MSS-CRC who have limited available treatment options as determined by the Investigator.

Part 2A of the study will investigate the anti-tumor activity of TSR-033 and dostarlimab in combination in participants with advanced or metastatic MSS-CRC. While the primary objective of this part of the study is ORR by Investigator assessment, copies of scans will be collected and stored at a repository for potential evaluation.

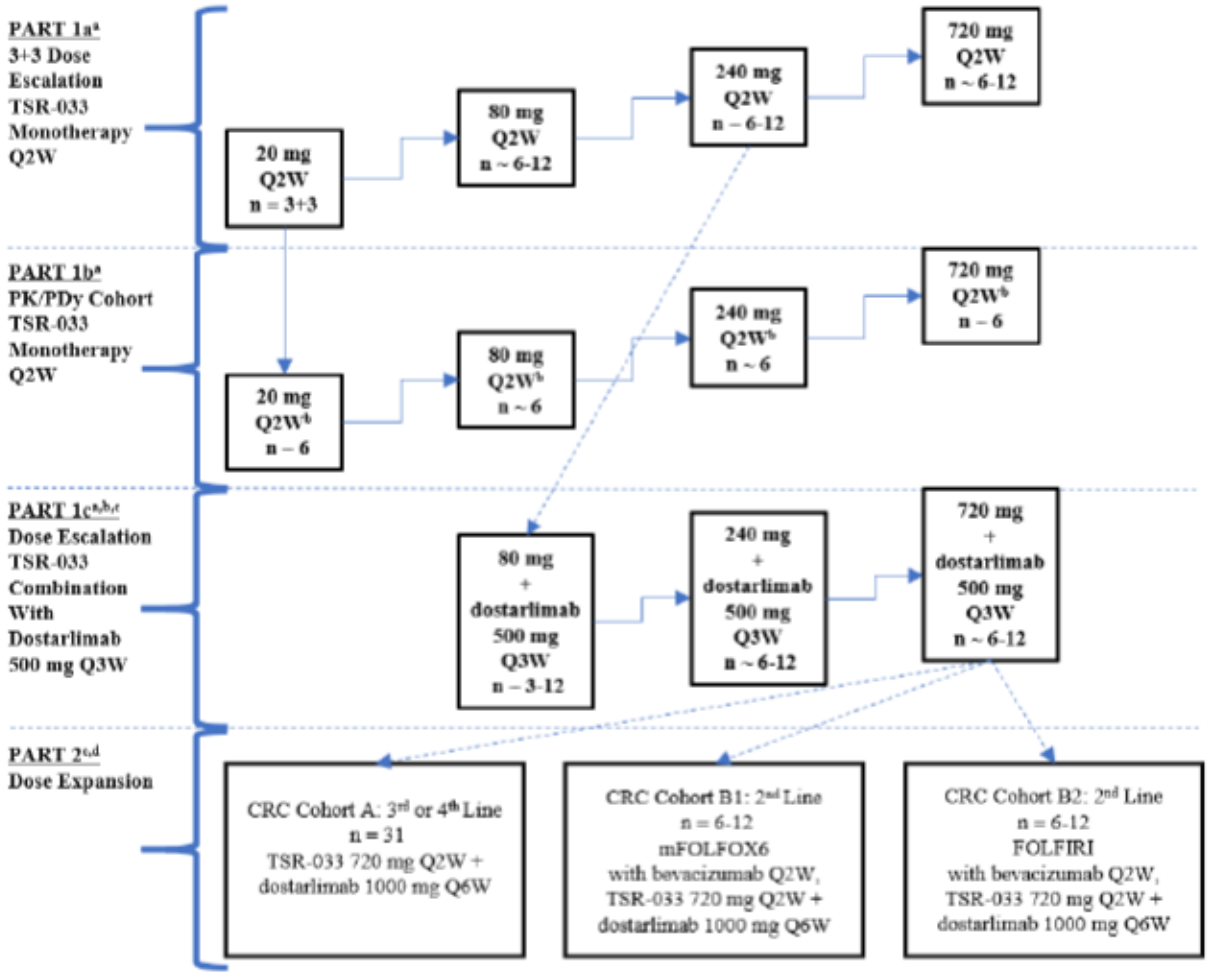
Part 2B of the study will investigate the safety and anti-tumor activity of TSR-033 and dostarlimab in combination with chemotherapy (Cohort B1: mFOLFOX6, Cohort B2: FOLFIRI) and bevacizumab in participants with advanced or metastatic MSS-CRC. As the primary objective of this part of the study will be safety, both Part 2B Cohorts will begin by enrolling 6 participants each, with enrollment being paused until the end of the DLT observation period before any further enrollment in this arm. While the secondary objective of this part of the study is ORR by Investigator assessment, copies of scans will be collected and stored at a repository for potential evaluation.

Toxicities will be assessed according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

The study will be conducted in conformance with Good Clinical Practice (GCP).

The design schema presented below (starting doses for Part 1b, Part 1c, and Part 2 are contingent on safety findings in earlier cohorts).

Figure 1 Study Design Schema



Abbreviations: CRC = colorectal cancer; DLT = dose-limiting toxicity; mg = milligrams; PDy = pharmacodynamics; PK = pharmacokinetics; Q2W = every 2 weeks; Q3W = every 3 weeks; Q6W = every 6 weeks; RP2D = recommended Phase 2 dose

a. Approximately 72 participants in Parts 1a, 1b and 1c are expected, but this may increase to approximately 132 participants in total if the sponsor and investigators determine that additional safety and/or PK[CCI] data are needed to confirm the RP2D for monotherapy. These enrollment numbers could increase if the Sponsor, in consultation with the Investigator, determine that additional cohorts consisting of 6-12 participants are needed to examine additional dose levels. At any dose level, where DLTs were observed in less than ⅓ of participants, in Part 1b, up to 6 additional participants may be enrolled to enable a better characterization of the PK[CCI] data in order to confirm the RP2D. These enrollment numbers could further increase if the Sponsor, in consultation with the Investigators determine that an intermediate dose level(s), consisting of approximately 6 participants requires exploration to better understand PK[CCI].

b. The starting dose of TSR-033 when used in combination with dostarlimab must be one dose level below the highest dose at which <⅓ of 6-12 participants experienced DLTs with single-agent TSR-033.
c. Doses presented in the schema represent the planned TSR-033 dose levels (subject to change based on safety and/or PK[redacted] data). dostarlimab will be given at a dose of 500 mg (Q3W) in Part 1c and 1000 mg Q6W in Part 2 of the study. These enrollment numbers could increase if the Sponsor, in consultation with the Investigator, determine that additional cohorts consisting of 6-12 participants are needed to examine additional dose levels.
d. Part 2 will enroll 2 disease-specific cohorts: Cohort A (third- or fourth-line MSS-CRC) and Cohort B (second-line MSS-CRC). The opening of enrollment of the expansion cohorts may not be simultaneous and is dependent on emerging data from ongoing studies.

1.2.2 Study Part 1

Study Part 1 consists of three stages: Part 1a, Part 1b, and Part 1c.

Part 1a (monotherapy dose escalation) will evaluate TSR-033 at ascending doses (20 mg, 80 mg, and 240 mg). A higher dose level of 720 mg, or intermediate dose levels may be explored, if warranted based on target exposure and safety findings. TSR-033 will be administered via 30-minute, IV infusion Q2W. The DLT observation period in Part 1a is defined as 28 days, encompassing 2 Q2W administrations of TSR-033.

Cohorts will be enrolled sequentially and will initially follow a 3+3 design at a starting dose of 20 mg, as determined by preclinical safety and pharmacology studies. Initially, 3 participants will be administered TSR-033, and dose escalation or expansion to 6 participants will be considered after all 3 participants at the 20-mg level have completed the DLT observation period and are found to be evaluable for safety upon review of safety data conducted by the Investigators and Sponsor. In subsequent dose levels, 6 participants will initially be enrolled into each cohort to evaluate ascending doses of TSR-033. At any dose level where DLTs are observed in ⅓ of participants, up to 6 additional participants may be enrolled in that dose level. The potential enrollment of additional participants will take place following discussion with the Investigators, taking into account severity and duration of observed DLTs as well as the overall safety of a dose level.

At any dose level, an initial 3 or 6 participants will be enrolled, then:

- If the observed DLT rate is <⅓, the dose may be escalated.
- If the observed DLT rate is >⅓, no further dose escalation will be considered, and this dose level will be considered the maximum administered dose (MAD).
- If the observed DLT rate is ⅓, the Sponsor may enroll up to 6 additional participants following discussion with the Investigators.

- If the observed DLT rate in a total cohort of 9 to 12 participants is >⅓, no further dose escalation will be considered, and this dose level will be considered the MAD.

The MTD will be considered the dose one level below the MAD if ≥⅓ of participants experience DLTs, or, at MAD if <⅓ of participants experience DLTs.

Accordingly, the RP2D may be at the MAD or 1 dose level below the MAD. Alternatively, an intermediate dose level below the MAD may be introduced and assessed for DLTs. Dose escalation will continue until the RP2D is identified or may be stopped at any dose level based on emerging safety and PK[redacted] data, subject to agreement between the Investigators and Sponsor. A RP2D will be defined as the dose with DLTs observed in <⅓ of at least 6 participants and desired PK [redacted] characteristics as determined by the Sponsor, in agreement with the Investigators. A participant will be considered non-evaluable if, for any reason other than safety, the participants is unable to complete the DLT observation period, or if the PK assessments were insufficient to define the PK profile. Participants in Part 1a considered non-evaluable may be replaced after consultation between the Investigators and Sponsor.

Part 1b (PK[redacted] Cohort): To better characterize the PK profile [redacted] from blood and tumor tissue samples following TSR-033 treatment, an additional cohort of participants (up to 6 participants per dose level) may subsequently be enrolled at a dose level with DLTs observed in <⅓ of participants. The potential enrollment of additional participants will take place following discussion with the Investigators, taking into account severity and duration of observed DLTs, as well as the overall safety of a dose level. These participants will begin treatment with TSR-033 on Day 1, followed by on-treatment visits during the following 28 days for safety assessments and blood sampling for PK[redacted]. Participants will receive their second dose of TSR-033 on Day 29 and every 14 days thereafter (Q2W). These additional participants will not be considered evaluable for dose escalation purposes (ie, not included into the DLT-evaluable population), but will contribute to the overall safety assessment at the dose level being evaluated

Participants enrolled in this cohort are required to have tumor tissue available (archival or newly obtained biopsy) prior to start of study treatment and must consent to undergo additional tumor biopsy approximately 4 to 6 weeks after initiating study treatment, and at the end of treatment (EOT) visit (for participants with progressive disease [PD]).

Part 1c (TSR-033 in Combination with dostarlimab): The starting dose of TSR-033 when used in combination with dostarlimab must be 1 dose level below the highest dose at which <⅓ of at least 6 participants experienced DLTs with single agent TSR-033.

TSR-033 will be administered with dostarlimab Q3W throughout Part 1c, and participants will receive dostarlimab at a dose of 500 mg in combination with ascending doses of TSR-033 Q3W. The starting dose of TSR-033 when used in combination with dostarlimab must be one dose level below the highest dose at which <⅓ of participants experienced DLTs with single-agent TSR-033. Planned dose levels of TSR-033 include 80 and 240 mg. A higher dose level of 720 mg Q3W may be explored if warranted based on target exposure and safety findings. Additional cohorts consisting of 6-12 participants are needed to examine additional dose levels may also be explored if warranted following agreement between the Investigators and Sponsor. dostarlimab at a dose of 1000 mg may also be tested with the RP2D of TSR-033 given on a Q6W schedule. For all administrations of the combination regimen, TSR-033 will be given first, followed by dostarlimab.

1.2.3 Study Part 2

Part 2 will commence using the RP2D established for the combination regimen in Part 1c of the study. Study treatment in Part 2 will be administered on a Q2W schedule for TSR-033 and a Q6W schedule for dostarlimab. In Part 2B, TSR-033 and dostarlimab will be administered on Day 3 of a dose cycle following chemotherapy and bevacizumab therapy on Day 1 of a dose cycle.

The expansion cohorts will evaluate the preliminary activity of TSR-033 in combination with dostarlimab in anti-PD-1 naïve participants with a specific tumor type as follows:

- Cohort A – Third- and fourth-line MSS-CRC
- Cohorts B1 and B2 – Second-line MSS-CRC

For Cohorts B1 and B2, if within 12 weeks of initiating study treatment, delayed irAEs consistent with DLT criteria occur in ≥⅓ of participants at a particular dose level, a lower dose level will be considered by the Sponsor following discussion with study Investigators for:

- Further refinement of RP2D and dose for expansion cohorts and/or
- All participants on treatment if in the best interest of the participant

1.2.4 Randomization Methodology

Randomization is not applicable in this study.

1.2.5 Stopping Rules and Unblinding

Prespecified stopping rules are included for dose escalation in Part 1 as per the modified 3+3 design.

Unblinding is not applicable as this is an open-label uncontrolled study with dose escalation in Part 1 and parallel single-arm cohorts in Part 2.

1.2.6 Study Procedures

Refer to the latest protocol amendment for the schedule of assessments.

1.2.7 Efficacy, Safety, and Pharmacokinetic parameters

1.2.7.1 Primary parameters

Study Part 1

- DLTs of TSR-033
- DLTs of TSR-033 in combination with dostarlimab

The maximum tolerated dose (MTD) is defined as the highest dose observed in at least 6 participants with DLTs in less than one-third of participants throughout the DLT observation period.

The RP2D will be based on the DLTs, overall safety, and PK[CCI] data of TSR-033 as a monotherapy and in combination with dostarlimab. The RP2D dose of TSR-033 as a monotherapy may differ from the RP2D dose used in combination.

Study Part 2

- 2A: ORR using RECIST v1.1 based on Investigator assessment
- 2B1 and 2B2: DLTs

Objective response rate (ORR) is defined as the proportion of participants whose best objective response (BOR) is a confirmed CR or confirmed PR.

BOR is defined as the best response between the date of first dose and the date of first documented progression or the date of subsequent anti-cancer therapy or the date of death, whichever occurs first. For participants without documented progression or subsequent anti-cancer therapy and alive at the time of analysis, all available response data will contribute to the BOR determination.

1.2.7.2 Secondary parameters

Efficacy parameters

In Part 1 and Part 2, unless otherwise specified:

- ORR by RECIST v1.1 (Part 1 and Part2B)
- DOR, DCR

For participants with confirmed CR or PR, DOR is defined as the time from first documented response until the time of first documentation of disease progression or death, whichever occurs first. Censoring rules of DOR are summarized in Section 4 (Table 5). For participants with stable disease (SD) as BOR, duration of stable disease

(DOSD) is defined as the time from the date of first dose to the date of the first documented tumor progression or death, whichever occurs first. Censoring rules will be the same as for DOR analysis.

DCR is defined as the proportion of participants whose BOR is a confirmed CR, confirmed PR, or SD. According to the protocol, SD is defined as to meet a minimum duration of 12 weeks (+/- 14 days) from the date of first dose.

Safety parameters

- DLTs
- Treatment emergent adverse events (TEAE)
- Changes in clinical laboratory parameters (hematology, chemistry, thyroid function)
- ECOG performance status
- ECG parameters
- Concomitant medications
- Immunogenicity: anti-TSR-033 antibodies

1.2.7.3 PK parameters

- Serum PK AUC from time 0 to last assessment (AUC0-last), AUC from time 0 to infinity (AUC0-∞), AUCtau, minimum concentration (Cmin), maximum concentration (Cmax), clearance (CL), volume of distribution (Vz), volume of distribution at steady state (Vss) and terminal half-life (t1/2), if data permit.

2 PATIENT POPULATION

2.1 Population Definitions

Analysis populations will be defined as follows for Part 1 and Part 2, respectively:

- Screened Population: All participants who were screened for eligibility.
- Enrolled Population: All participants who sign the informed consent and entered the study. Screening failures (who never passed screening even if rescreened) are excluded from the Enrolled analysis set as they did not enter the study.
- Safety Population: All participants who receive any amount of any study drug (TSR-033, TSR-042, mFOLFOX6 or FOLFIRI).
- Efficacy Population: All participants who receive any amount of TSR-033.
- DLT Evaluable Population: The assessment of DLTs in Part 1a, Part 1c, and Part 2B will include only those participants completing the DLT observation period throughout the course of 2 TSR-033 administrations (ie, Day 1 and Day 15 in the first 28 days of study treatment) for Part 1a, the course of 2

TSR-033 + dostarlimab administrations (ie, Day 1 and Day 21 in the first 42 days of study treatment) for Part 1c, the course of 2 TSR-033 + dostarlimab administrations (ie, Day 3 and Day 17 in the first 30 days of study treatment) unless the participant discontinued TSR-033 (Part 1a) or TSR-033 + dostarlimab (Part 1c and Part 2B) due to a DLT.

- Per Protocol Population: All participants in the Efficacy Population who have no major (i.e. important) protocol violations during the study and have ⩾1 post-baseline disease assessment.
  This population may be used for the efficacy assessment of cohort 2A after reviewing important protocol deviations during DBR.
- Pharmacokinetic (PK) Population: All participants who receive any amount of TSR-033 and/or dostarlimab and have at least 1 measurable drug concentration.
- Immunogenicity (ADA) Population: The immunogenicity population includes all participants who receive at least 1 dose of TSR-033 and who have at least 1 ADA sample with a result.

2.2 Protocol Deviations

Protocol deviations (PDv) will be assessed and classified as important per Sponsor's SOP. If a reported PDv does not meet classification criteria for importance, the PDv will be reported as a protocol deviation without a classification.

- A PDv is classified as important if it is confirmed to adversely impact the completeness, accuracy, and/or reliability of the study data, or affect a subject's rights, safety, or well-being.

All PDvs will be identified and finalized prior to database lock. Important PDvs would result in a participant being excluded from the PP population.

Examples of important protocol deviations and any action to be taken regarding the exclusion of participants or affected data from specific analyses are outlined below.

Significant Protocol Deviation (Example)	**Population Exclusions**
Failed to meet eligibility criteria but entered study	Exclude from PP
Non-compliant with study medication other than as allowed by protocol	Exclude from PP
Took prohibited concomitant medication that impacts efficacy	Exclude from PP

The following PDv outputs will be provided using the Enrolled population:

- Number and percentage of participants with an important protocol deviation by type of deviation.
- Number and percentage of participants with an important protocol deviation by relationship (related, not related) to COVID-19 pandemic
- A listing of all protocol deviations
- A listing of all non-important COVID-19 related protocol deviations

3 GENERAL STATISTICAL METHODS

3.1 Sample Size Justification

Ascending doses of TSR-033 in Part 1a and in combination with dostarlimab in Part 1c will be evaluated to identify the respective RP2Ds. The actual number of participants accrued during this phase will be determined largely by the safety and PK findings observed during the course of their treatment. RP2D decisions for Part 1a and Part 1c will be based on a minimum of 6 participants for each regimen. Participants in Part 1b (PK[redacted] cohort) will not be considered evaluable for dose escalation purposes (ie, not included into the DLT-evaluable population), but will contribute to the overall safety assessment at the dose level being evaluated. It is expected that up to approximately 132 participants will be enrolled in Part 1 as follows:

Part 1a (TSR-033 monotherapy dose escalation): Approximately 30-54 participants

Part 1b (TSR-033 monotherapy PK[redacted] characterization): Approximately 18-30 participants

Part 1c (TSR-033 + dostarlimab combination dose escalation): Approximately 24-48 participants

A total of up to approximately 55 participants are anticipated in the expansion cohorts in Part 2.

Part 2A (TSR-033 + dostarlimab combination dose expansion in anti-PD-1-naïve third- or fourth-line MSS-CRC participants): A null hypothesis of ORR 10% will be tested against an alternative hypothesis of ORR 25%. The trial is designed using a one-sided exact test that achieves a minimum of 80% power at alpha level of 0.1. A sample size of 31 will provide an attained power of 82.4% and an attained type-1 error of 0.083. The null hypothesis will be rejected if 6 or more responses are observed in the 31 participants.

Part 2B (TSR-033 + dostarlimab combination given with mFOLFOX6 or FOLFIRI and bevacizumab [SOC] in anti-PD-1-naïve second-line MSS-CRC participants): A null hypothesis of ORR 20% will be tested against an alternative hypothesis of ORR 40%. The trial is designed using a one-sided exact test that achieves a minimum of 80% power at alpha level of 0.1. A sample size of 24 will provide an attained power of 80.8% and an

attained type-1 error of 0.089. The null hypothesis will be rejected if 8 or more responses are observed in the 24 participants.

3.2 General Methods

All descriptive statistics and statistical analyses will be performed using the most recently released and available SAS statistical software, unless otherwise noted. All outputs will be incorporated into Microsoft Word or Excel files or Adobe Acrobat PDF files, sorted and labeled according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) recommendations, and formatted to the appropriate page size(s).

Tables, listings, and figures will display data overall and by dose level, separately for each part in the following order unless otherwise specified: Part 1ab, Part 1c, Part 2A, Part 2B1, and Part 2B2.

All safety analyses will be performed for any participant who received any amount of any study drug. All analyses for efficacy will use Dose 1, Day 1 as the reference start time.

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters.

For categorical variables, summary tabulations of the number and percentage of participants within each category of the parameter will be presented. Percentages will be based on the participants with a non-missing parameter unless missing category is presented. Percentages will be reported to one decimal place. Percentages will not be presented for zero counts.

For continuous variables, the number of participants, mean, standard deviation, median, first quartile (Q_1), third quartile (Q_3), minimum, and maximum values will be presented. Mean, median, Q_1, and Q_3 will be reported to 1 more decimal place than the raw data, while the standard deviation will be reported to 2 more decimal places than the raw data. Minimum and maximum will have the same number of decimal places as the raw data.

Time-to-event data will be summarized using Kaplan-Meier (KM) methodology using 25^{th}, 50^{th} (median), and 75^{th} percentiles with associated 2-sided 95% confidence intervals (CIs), as well as percentage of censored observations.

Formal statistical hypothesis testing will be performed on the primary and/or secondary efficacy endpoint as described in the protocol.

All data listings that contain an evaluation date will also contain a relative study day.

Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study drug which is designated as Day 1. The preceding day is Day -1, the day

before that is Day -2, etc. Post-treatment study days are numbered relative to the first dose and are designated as Day +1, Day +2, etc. The last day of study drug is designated with an "L" (e.g., Day 14L). In addition to relative day, cycle and day of treatment within cycle will be calculated and presented when applicable.

In addition:

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v24.1 or later.

Laboratory parameter changes will be described using shift tables, relative to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

- Concomitant medications will be coded using the latest version of the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification (dated March 2021 or later).
- P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001"
- CIs will be presented to one more decimal place than the raw data
- Weeks will be calculated as Number of days divided by 7
- Months will be calculated as Number of days divided by 30.4375
- Years will be calculated as Number of days divided by 365.25
- Day 1 will be considered as the first day of treatment
- End of Study is defined as the last available post-treatment assessment
- For the laboratory data if the parameter value is collected as '<xx' or '>xx', then the corresponding integer after the '<' or '>' symbol will be used for summarizing the data.
- All tables, figures, and listings will include footers at the bottom of the page reflecting the path and date of the datasets, datasets used to generate the tables, figures, and listings, and date and time of the generation of the output.

3.3 Baseline Definitions

For all analyses unless otherwise noted, baseline is defined as the most recent non-missing measurement prior to the first administration of study drug. Baseline can be the same date as first dose, given the measurement is expected prior to first dose when only date information is available.

3.4 Methods of Pooling Data

Data will be pooled across study sites. When applicable, data from all disease cohorts will be pooled to provide an integrated summary.

3.5 Adjustments for Covariates

No formal statistical analyses that adjust for possible covariate effects are planned for the efficacy or safety endpoints.

3.6 Multiplicity Adjustment

Multiplicity is not adjusted in this study.

3.7 Subpopulations

Not applicable.

3.8 Withdrawals, Drop-outs, Loss to Follow-up

After consultation between the Investigators and Sponsor, enrollment may be extended to replace participant(s) that become non-evaluable for DLT evaluation, safety or if there is insufficient PK data during Part 1.

In Part 2, if a participant discontinues study treatment prior to the first assessment of disease (either scheduled radiological assessment at 6 weeks post treatment initiation or clinically indicated disease assessment prior to 6 weeks), the participant may be replaced after consultation between the Investigators and Sponsor unless the participant discontinued study treatment due to clear clinical progression without radiographic evidence of progression. In these participants, obtaining a subsequent confirmatory radiographic image is necessary if feasible (eg, participant's condition allows for imaging).

3.9 Missing Data

In general, there will be no imputations made to accommodate missing data points. All data recorded on the eCRF will be included in data listings for the CSR.

The following rules will be applied if there are values that are below the lower limit of quantification (BLQ) or if there are missing values (e.g., no result [NR]) in a plasma concentration data series to be summarized.

- In summary statistics, BLQ values will be set to zero.
- In categorical summary, BLQ category will be listed.
- NR result will be set to missing.

When tabulating AE data, partial dates will be handled as follows.

- If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as study treatment start date. In this case, in order to conservatively report the event as treatment-emergent, the onset date will be assumed to be the study treatment start date.
- If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the study treatment

start date. In this case, the event onset will be coded to the day of treatment in order to conservatively report the event as treatment-emergent.

- A missing onset date will be coded as the study treatment start date. If the resulting onset date is after a reported date of resolution, the onset date will be set equal to the date of resolution.
- Imputation of partial dates is used only to determine whether an event is treatment-emergent; data listings will present the partial date as recorded in the eCRF.
- For initial diagnosis and prior anti-cancer treatment for primary cancer, partial dates will be handled as follows:

  For start dates:

  - If the day of the month is missing, the day will be imputed with the first day of the month.
  - If both the day and month are missing, the day and month will be assumed as first day of the year i.e. January 1.

  For end dates:

  - If the end day is missing, the day will be imputed to the last day of the month.
  - If both the end day and month are missing, the day and month will be assumed as last day of the year i.e. December 31.
  - If the imputed end date is after the first dose date of study treatment, use the first dose date as the imputed end date.
- Incomplete start date of follow-up anti-cancer treatment will be imputed as follows:
  - If only ‘day’ is missing, then impute day with last day of the month.
  - If ‘day’ and ‘month’ are missing, and ‘year’ is not missing or the same as the year of last dose, then impute as December 31st.
  - If the imputed start date is greater than last contact date, then set to last contact date.
- For disease progression, partial dates will be handled as follows:
  - If the day is missing
    - If the progression month and year is the same as the last treatment stop month and year, the progression day will be set to the last treatment stop day
    - If the progression month and year is after the last treatment stop month and year, the progression day will be set to the first day of the month of progression
  - If both the day and month are missing
    - If the progression year is the same as the last treatment stop year, the day and month will be set to the last treatment stop day and month

        - If the progression year is after the last treatment stop year, the day and month will be set to the first day and month of the year.
    - If day, month, and year are missing, no imputation is needed.

3.10 Visit Windows

All participants will undergo serial radiographic assessments to assess tumor response. Initial tumor imaging at screening must be performed within 28 days prior to the date of the first dose of study treatment. Scans performed prior to the signing of the ICF as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and performed within 28 days prior to first dose date.

Tumor imaging should be performed Q6W (42 ±7 days) for the first 3 assessments and then every 9 (63 ±7 days) weeks thereafter, or more frequently if clinically indicated and at the time of suspected PD. After 1 year of radiographic assessments, participants will have imaging performed every 12 weeks (84 ±7 days). Imaging should not be delayed for delays in dosing.

Continue to perform imaging until whichever of the following occurs:

- The start of new anti-cancer treatment
- Withdrawal of consent
- Death
- End of the study (when responder or discontinuation status for all participants is known)

Participants who discontinue study treatment for reasons other than PD will continue post-treatment imaging studies for disease status FUP at the same frequency as already followed (every 6, 9, or 12 weeks [±7 days] depending on the length of treatment with the study drug) until PD, start of a non-study anti-cancer treatment, withdrawal of consent to study participation, loss to FUP, death, or end of the study.

By-visit summaries and analyses will be performed by nominal visit. All data will be tabulated per the evaluation visit as recorded on the eCRF even if the assessment is outside of the visit window for analysis. In data listings, the relative day of all dates will be presented.

3.11 Interim Analysis

No formal interim analysis is planned for this study. However, a review of safety data and available preliminary PK data will be conducted by the Sponsor and Investigators following completion of the DLT observation periods in Part 1a and Part 1c. Determination of the RP2D will be based on review of safety, PK, and [redacted] data.

4 STUDY ANALYSES

4.1 Participant Disposition

Participant disposition will be tabulated and include the numbers of screened and enrolled participants, the number treated in total, the number in each analysis population, the numbers who discontinued treatment and discontinued study and reason(s) for withdrawal, and the number of participants who died. Participant disposition will be summarized for the Enrolled population using descriptive statistics.

A by-participant data listing of study completion information including the reason of study withdrawal will be presented.

4.2 Demographics, Baseline Characteristics and Medical History

Demographics, baseline characteristics, and medical history information will be summarized for the Safety population in Part 1 and Efficacy population in Part 2 using descriptive statistics. No formal statistical comparisons will be performed.

Demographic and baseline data for each participant will be provided in data listings.

The demographic and baseline characteristics tables will include the following variables:

- Gender
- Age at time of screening (years) calculated as date of screening minus date of birth / 365.25 if date of birth is reported, or age as reported on the eCRF will be used
- Age categories ($\leq$18, 19 to 64, $\geq$ 65)
- Race (White, Black, Asian, American Indian/Alaska Native, Native Hawaiian or other Pacific Islander, Other, Unknown, and Not Reported)
- Ethnicity (Hispanic or Latino, non-Hispanic or Latino, Unknown, and Not Reported)
- Time from first diagnosis to first dose of study drug (years)
- Primary tumor site
- Baseline weight (in kilograms, last non-missing value prior to first dose; if weight is reported in pounds, convert to kilograms by dividing by 2.2)

  Baseline height (in centimeters, last non-missing value prior to first dose; if height is reported in inches, convert to centimeters by multiplying by 2.54)

- Baseline body mass index (BMI) (kg/m^2), calculated using the participant's height and weight at screening [BMI (kg/m^2) = weight (kg) / height (m)^2]
- ECOG performance status at baseline
- Prior cancer treatment including number of prior treatments. For Part 2 of the study, prior anti-cancer treatment will be defined as any prior regimen where:
    - Extent of disease is metastatic, and reason is palliative
    - OR Extent of disease is locoregional, reason is neoadjuvant or adjuvant, and last prior anti-cancer treatment stop date is within 1 year of date of enrollment
- Histology and grade of disease at diagnosis
- Best response during last treatment
- Months from start of last treatment to progression or recurrence calculated as the date of recurrence after the last treatment minus the start date of last treatment +1 divided by 30.4375
- Months from end of last treatment to first dose of study drug calculated as the date of first dose minus end date of last treatment +1 divided by 30.4375

Prior anti-cancer therapy, medical history and prior and concomitant medications will be summarized. Medical history will be coded using MedDRA v24.1 or later, and the number and percentage of participants experiencing at least one such diagnosis by MedDRA preferred term (PT) will be reported.

COVID-19 cases will be captured on the COVID-19 CRF based on the WHO criteria using the categories of: suspected, probable, and confirmed cases. The COVID-19 infected subpopulation will be summarized in a table including the number of subjects with suspected, probable, or confirmed COVID-19 diagnosis and the number of subjects who had a diagnosis test performed with the number of subjects with positive, negative, or indeterminate results.

4.3 Efficacy Evaluation

Efficacy analyses will be conducted in the Efficacy population unless stated otherwise.

4.3.1 Primary Efficacy Endpoint (ORR)

In Study Part 2A, the primary efficacy endpoint is ORR, defined as the proportion of participants who have achieved confirmed CR or PR using Investigator assessment per the RECIST v1.1 criteria.

In Study Part 2B, ORR will also be evaluated by combining cohort 2B1 and 2B2 using Investigator assessment per the RECIST v1.1 criteria.

Tumor assessments should be made at each time point specified in the protocol: every 6 weeks (42±7 days) for the first 3 assessments and then every 9 weeks (63±7 days) thereafter while on study treatment, or more frequently if clinically indicated and at the time of suspected PD. After 1 year, tumor assessments may be performed every 12

weeks (84±7 days) until disease progression or death or discontinuation from study. Tumor imaging for confirmation of response may be performed at the earliest 28 days after the first indication of response.

A summary of criteria for the target lesions and the non-target lesions at each tumor assessment is included in Table 2 and Table 3. For participants who have measurable disease at baseline, Table 4 provides a summary of the overall response status at each time point. For participants who are enrolled in this study without measurable disease, Table 5 will be used to evaluate those participants at each time point. As confirmed CR/PR is required in the protocol, the best overall response (BOR) will be determined as shown in Table 6.

Table 2 RECIST v1.1 Response Criteria of Target Lesions at Each Assessment

Tumor assessment	
CR	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
PR	At least 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
PD	At least 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Table 3 RECIST v1.1 Response Criteria of Non-Target Lesions at Each Assessment

Tumor assessment	
CR	Disappearance of all non-target lesions and normalization of tumor marker level. Any lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PR	Persistence of one or more non-target lesions(s) and/or maintenance of tumor marker level above the normal limits.
PD	Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Table 4 RECIST v1.1 Overall Response at Each Assessment for Participants with Measurable Disease at Study Entry

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-CR/Non-PD/Not evaluated	No	PR
SD	Non-CR/Non-PD/Not evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
Not all evaluated	Non-PD	No	NE

Table 5 RECIST v1.1 Overall Response at Each Assessment for Participants without Measurable Disease at Study Entry

Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/Non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Table 6 RECIST v1.1 Best Overall Response when confirmation of CR and PR required

Overall Response first timepoint	Overall Response subsequent timepoint	Best Overall Response
CR	CR	CR provided minimum criteria for CR met, otherwise, SD provided minimum criteria for SD met, otherwise, NE
CR	PR	SD provided minimum criteria for SD duration met, otherwise, PD
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR provided minimum criteria for PR met, otherwise, SD provided minimum criteria for SD met, otherwise, NE
PR	PR	PR provided minimum criteria for PR met, otherwise, SD provided minimum criteria for SD met, otherwise, NE
PR	SD	SD provided minimum criteria for SD duration met, otherwise, NE
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
SD	SD	SD provided minimum criteria for SD duration met, otherwise, NE
SD	PD	SD provided minimum criteria for SD duration met, otherwise, PD
SD	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

Note: Minimum 12 weeks (84 - 14 = 70 days) for SD and at least 28 days for CR/PR.

For each participant, BOR will be determined based on the overall responses at all time points between the date of first dose and the date of first documented progression, or the date of subsequent anti-cancer therapy, or the date of study discontinuation, whichever occurs first.

Specifically:

- Day 1 can be determined from the “date of infusion” field on the “Infusion Study Treatment” form.

- The date of disease progression can be determined by selecting the earliest date from the "date of the radiological scan or assessment on which the response evaluation was based" field on the "evaluation of response (RECIST)" form where "overall response" = PD.
- Subsequent anti-cancer therapy can be determined by checking for any entries made on the "follow up anti-cancer therapy" form.
- The date of study discontinuation can be determined by using the "date of study discontinuation" field on the "discontinuation of study" form.
- For each participant, select all "evaluation of response (RECIST)" forms meeting the following criteria:
    - The "date of the radiological scan or assessment on which the response evaluation was based" is after Day 1.
    - The "date of the radiological scan or assessment on which the response evaluation was based" is on or before the date of disease progression, date that anti-cancer therapy first began, and the date of study discontinuation. If the participant did not experience disease progression, begin anti-cancer therapy, or discontinue the study prematurely, select all forms after Day 1.

Participants with a BOR of either confirmed CR or confirmed PR are considered to have responded to treatment ("responders") for the primary efficacy variable (ORR). All other participants are considered to have not responded to treatment ("non-responders") for the primary efficacy variable.

The point estimate and two-sided 95% CI for the ORR will be calculated. The exact (Clopper-Pearson) method will be used to calculate the two-sided 95% CI. This can be programmed in SAS by appending the "/ BINOMIAL (EXACT)" option to the end of the appropriate "TABLE" statement.

Summary tables will be generated in the Efficacy population for all cohorts. The following figures will be generated for the cohorts in Part 2 only:

- Tumor burden (sum of longest diameters of target lesions) will be presented graphically using waterfall plots, to present each subject's best percentage change in tumor size as a separate vertical bar, with the bars ordered from the largest increase to the largest decrease. BOR for each subject will be presented above or below each bar along with indicators for new lesions.
- Tumor burden (sum of longest diameters of target lesions) will also be presented graphically using spider plots, to present each subject's percentage change in tumor size over time as a separate line along with indicators for new lesions.

Unconfirmed ORR may also be evaluated as needed. Participants with a BOR of either CR or PR are considered to have responded to treatment ("responders") for the evaluation of unconfirmed BOR. All other participants are considered to have not responded to treatment ("non-responders").

4.3.2 Secondary Efficacy Endpoint

KM summary tables and figures will only be produced for the cohorts in Part 2.

4.3.2.1 Duration of response (DOR) based on RECIST v1.1

For participants who responded to treatment, DOR (in months) will be calculated as:

[Earliest date of PD or death – Earliest date of confirmed CR or PR + 1] / 30.4375

Table 7 provides a summary of the censoring rules used in primary analysis of DOR. A time-to-event analysis of DOR will be performed using KM methods including quartile/median estimates and associated 95% CIs. A KM plot will be produced.

Table 7 Censoring rules used in DOR analysis

Situation	Date of Event or Censoring	Outcome
Start of subsequent anti-cancer therapy prior to a documented progression or death	Date of last evaluable radiologic tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy	Censored
Free of progression and no subsequent anti-cancer therapy started and no death	Date of last evaluable radiologic tumor assessment	Censored
Documented progression or death after two or more consecutive missing radiologic assessments	Date of last evaluable radiologic tumor assessment prior to the two or more consecutive missing radiologic assessments	Censored
Documented progression or death	Earliest date of documented tumor progression or death	Event

4.3.2.2 Disease control rate (DCR) based on RECIST v1.1

Participants who achieved a best overall response rate of confirmed CR/PR confirmed with at least 28 days duration, or SD confirmed with a minimum of 12 weeks duration (84-14=70 days), will be considered “responders” for this endpoint. All other participants will be considered “non-responders” for this endpoint.

Since radiographic evaluations to assess extent of disease will be conducted every 6 weeks (42±7 days), the minimum of 12 weeks duration for confirmed SD corresponds to 2 consecutive scans (i.e. at least 84-14= 70 days). For confirmed CR/PR, the two consecutive CR/PR assessments need to be at least 28 days apart.

Unconfirmed **DCR** may also be evaluated as needed.

The point estimate and two-sided 95% CI will be calculated. The exact (Clopper-Pearson) method will be used to calculate the 95% CI. This can be programmed in SAS

by appending the "/BINOMIAL(EXACT)" option to the end of the appropriate "TABLE" statement.

4.4 Safety Evaluation

The safety analyses will be based on the Safety population, unless otherwise specified.

4.4.1 Treatment Exposure and Compliance

Study treatment exposure and compliance will be summarized by dose level, phase of the study, including:

- Number of infusions as a continuous variable
- Number and percentage of participants treated by maximum number of infusions (1, 2, 3 … and ≥12)
- Duration of treatment (months), defined as
    - [last dose date - first dose date + duration of dosing interval (day)] / 30.4375
- Duration on study (months), defined as
    - [last contact date - first dose date + 1] / 30.4375, where last contact date is the last visit date or date of death.
- Number of participants with dose interruptions
- Number of participants with dose delays
- Intended cumulative dose (mg), defined as the sum of intended dose at each infusion.
    - If the intended dose is recorded in "mg/kg", then, intended dose at an infusion is = (intended dose in mg/kg) * weight of the subject in kg's.
    - Else if intended dose is recorded in "mg/m^2", then intended dose at an infusion is = (intended dose in mg/m^2) * BSA.

Where BSA (Body Surface Area) is calculated using DuBois formula,

$BSA(m^2) = 0.20247(\text{height in m})^{0.725}(\text{weight in kg})^{0.425}$

- Intended Dose Intensity (mg/dose) defined as,
    - Intended cumulative dose (mg) divided by the number of infusions.
- Actual cumulative dose (mg), defined as
    - Sum of all doses actually administered.
- Actual dose intensity (mg/dose), defined as
    - Actual cumulative dose (mg) divided by the number of infusions
- Relative dose intensity (%), defined as

Actual dose intensity (mg/dose) divided by the intended dose per infusion (mg/dose), expressed in percentage.

A by-participant listing based on the safety population will be produced.

Treatment Period (i.e. on-treatment)

The period from the date of first dose of study treatment up to and including 90 days after the EOT visit or the earliest date of subsequent anti-cancer drug therapy, whichever occurs first, unless otherwise stated.

4.4.2 Adverse Events

All AEs will be classified by PT using MedDRA v24.1 or later.

Any Treatment Emergent AEs (TEAEs) will be defined per protocol as:

- Any new AE (one that was not seen prior to the start of treatment) that occurs for the first time after at least 1 dose of study treatment has been administered until 90 days after cessation of study treatment (or until the start of alternative anti-cancer therapy, whichever occurs earlier); or,
- A preexisting condition (one that was seen prior to the start of treatment) that worsens in severity (according to the CTCAE grade) or subsequently is considered drug-related by the Investigator after at least 1 dose of study treatment has been administered until 90 days after cessation of study treatment (or until the stat of alternative anti-cancer therapy, whichever occurs earlier).

If the start date is missing for an AE and the actual start date cannot be determined from a partial date, the AE will be considered treatment-emergent.

All AEs will be collected from the time of signing the ICF until 90 days after cessation of study treatment (or until alternative anti-cancer therapy is initiated, whichever occurs first), and any pregnancies are to be captured through 150 days post-treatment. Any AEs recorded in the database that occur from the time of ICF to first dose will be listed only and not included in safety analyses. Pre-existing conditions will be recorded in the eCRF on the Medical History or appropriate page.

The severity of the toxicities will be graded according to the NCI CTCAE v5.0. Within the same MedDRA PT, only the most severe AE for each participant will be counted in tabulations by severity.

Related TEAEs are defined as TEAEs considered likely related or related to treatment as judged by the Investigator. Any AEs for which the relationship to study drug is missing will be considered as related to study treatment. Within the same MedDRA PT, only the AE with the highest ranked relationship to treatment for each participant will be counted in tabulations by relationship to treatment. The imputation for a missing relationship will take place prior to determining the most related AE within a SOC or PT for a given participant.

A high-level overview of TEAEs will be presented in a summary table. This table will include the number and percentage of participants for the following categories:

- any TEAE
- any related TEAEs
- any TEAEs with toxicity grade 3 or above
- any related TEAEs with toxicity grade 3 or above
- any treatment-emergent serious adverse events (SAEs),
- any related SAEs
- any TEAEs leading to treatment discontinuation
- any TEAEs leading to treatment interruption
- any TEAEs leading to death
- any related TEAEs leading to death

The number and percentage of participants reporting a TEAE will be summarized by PT, toxicity grade, and relationship to study drug, respectively. AE tabulations will be ordered in terms of decreasing frequency for PT.

The incidence of COVID-19 reported as an AE and SAE will be reported in the standard AE and SAE tables. The incidence of treatment discontinuation due to AE of COVID-19 infection will be reported in the table of TEAEs leading to treatment discontinuation.

The following AE tables will be produced.

- Overview of AEs
- DLTs by PT (Part 1)
- TEAE by PT (sorted by decreasing frequency)
- Related TEAE by PT (sorted by decreasing frequency)
- TEAE with toxicity grade 3 or above by PT
- Related TEAE with toxicity grade 3 or above by PT
- Treatment emergent SAEs by PT (sorted by decreasing frequency)
- Related treatment emergent SAEs by PT (sorted by decreasing frequency)
- TEAEs leading to treatment discontinuation by PT
- TEAEs leading to treatment interruption by PT
- TEAEs leading to death by PT
- Non-serious TEAEs ≥5% in the study arm (for clinicaltrials.gov)
- Exposure Adjusted Incidence rates of common TEAEs (≥5%) over the time course of the trial (pre, during, and post pandemic, as appropriate)
- Exposure Adjusted Incidence rates of Any TEAEs, any treatment emergent SAEs and Any Grade 3/4/5 TEAEs over the time course of the trial (pre, during, and post pandemic, as appropriate) by overall, country or analysis region, age group, and gender.

The definition of when COVID-19 Pandemic Measures Began is given in Appendix 7.2. Participants may be counted in more than one-time course of the trial (pre, during, and post pandemic, as appropriate). The number of subjects at risk at the start of the given time interval will be calculated.

Exposure adjusted incidence rate (rate/100 PY) = (number of participants with occurrence of a specific treatment emergent adverse event /total exposure duration in years across all participants at risk at the start of the given time interval) * 100, where exposure duration for each participant is calculated as:

- (treatment stop date – treatment start date + duration of dosing interval [day])/365.25 for participants who DO NOT experience the event
- (start date of first TEAE – treatment start date + 1)/365.25 for participants that DO experience the event.

For recurring events, the first occurrence of an event (by MedDRA PT) will be reported, with the appropriate corresponding exposure years.

Immune-related adverse events of interest (irAEs) are defined as any >= Grade 2 AEs based on a pre-specified search list of PTs.

The following AE tables will be produced for treatment emergent immune-related AEs irAEs by SOC and PT:

- irAEs by PT (sorted by frequency)
- irAEs with toxicity grade 3 or above by PT
- Serious irAEs by PT
- irAEs leading to treatment discontinuation by PT
- irAEs leading to death by PT

The following by-participant listings will be produced.

- All AEs
- DLTs
- Deaths
- Treatment emergent SAEs
- TEAEs leading to treatment interruption.
- TEAEs leading to treatment discontinuation
- irAEs

4.4.3 Laboratory Data

Laboratory assessments for safety oversight are performed locally at each center's laboratory by means of their established methods. All laboratory values will be converted to SI units and classified as normal, low, or high based on normal ranges supplied by the local laboratories and upon employing standardization.

NCI CTCAE v5.0 grades will be applied for the following lab parameters:

- Hematology: hemoglobin (anemia), WBC (leukopenia), lymphocytes (lymphopenia), neutrophils (neutropenia) platelets and (thrombocytopenia)
- Chemistry: albumin (hypoalbuminemia), alkaline phosphatase (alkaline phosphatase increased), ALT, AST, total bilirubin (blood bilirubin increased), corrected calcium (hypocalcemia, hypercalcemia), creatinine (creatinine increased), glucose (hyperglycemia, hypoglycemia), magnesium (hypermagnesemia, hypomagnesemia), potassium (hyperkalemia, hypokalemia), and sodium (hyponatremia, hypernatremia)

Where corrected calcium is derived with the following formula: Corrected calcium (mmol/L) = Serum calcium (mmol/L) + (0.02 * (Normal albumin (g/L) – Patient's albumin (g/L))) where normal albumin is 40 g/L.

Laboratory results will be summarized by maximum CTCAE grade as available. Continuous results will be analyzed using change from baseline and shift values.

A shift summary of baseline to maximum severity during the treatment period for all parameters noted above will be produced for the coded hematology and chemistry parameters. Participants without an assessment present at baseline or on-study treatment will be included as a missing category.

Shift from baseline to the smallest, largest, and EOT will be reported using number and percentage of participants.

Liver function tests during the treatment period will be summarized by the following categories.

- ALT ≥ 3×ULN, ALT ≥ 5×ULN, ALT ≥ 10×ULN, ALT ≥ 20×ULN
- AST ≥ 3×ULN, AST ≥ 5xULN, AST ≥ 10×ULN, AST ≥ 20×ULN
- (ALT or AST) ≥ 3×ULN, (ALT or AST) ≥ 5×ULN, (ALT or AST) ≥ 10×ULN, (ALT or AST) ≥ 20×ULN
- Total bilirubin ≥ 2×ULN
- Concurrent ALT ≥ 3×ULN and total bilirubin ≥ 2×ULN
- Concurrent AST ≥ 3×ULN and total bilirubin ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and total bilirubin ≥ 2×ULN

- Concurrent (ALT or AST) ≥ 3×ULN and total bilirubin ≥ 2×ULN and ALP > 2×ULN
- Hy's law: Concurrent (ALT or AST) ≥ 3×ULN and total bilirubin ≥ 2×ULN and ALP < 2×ULN or missing and concurrent measurements are those occurring on the same date.

A by- participant listing of all laboratory data will be provided, with laboratory reference ranges and abnormal values highlighted, and including center, participant identifier, and visit.

4.4.4 Electrocardiogram

Standard 12-lead ECGs will be performed locally for participants in the study. Any ECG findings that were assessed as clinically significant and were reported as an AE or SAE will be summarized in the AE tables and listings.

ECG results will be summarized descriptively. ECG measurements include Heart rate, PR interval, QT interval, RR interval, and QRS complex.

QTc will be used for the data analysis and interpretation. Commonly used techniques including Bazett's (QTcB) and Fridericia's (QTcF) methods are applied. QTcF will be used for the primary QT evaluation.

The following analyses will be performed during the treatment period:

- A summary of the number and percentage of participants with QTc interval exceeding some predefined upper limit (e.g., >450 ms, >480 ms, >500 ms) will be provided. A summary of the number and percentage of participants with change from baseline in QTc interval exceeding some predefined upper limit (e.g., >30 ms, >60 ms) will be provided.
- A separate summary will be provided which summarizes the change from baseline to the most extreme high or low value at any time during treatment.

Change from baseline will be summarized and analyzed according to the largest increase, decrease, and at EOT. Graphical line mean changes over time may be provided.

All ECG data for each participant will be provided in a data listing.

4.4.5 Concomitant Medications

Medications collected at Screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary (version 201809). Medication start and stop dates will be compared to the date of first dose of study drug to allow medications to be classified as Prior-only, Prior-and-Concomitant, or Concomitant-only. Medications starting after the treatment withdrawal date will be listed but will not be classified or summarized.

Medications that start and stop prior to the date of first dose of study drug will be classified as Prior-only. If a medication starts before the date of first dose of study drug and stops on or after the date of first dose of study drug then the medication will be classified as Prior-and-Concomitant. Medications will be classified as Concomitant-only if they have a start date on or after the date of first dose of study drug, but prior to the treatment withdrawal date. Concomitant medication will be summarized by ATC level 3 and PT in frequency tables by treatment. Participants with more than 1 medication in a given ATC level and PT will be counted only once in that category.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study drug. Medications will be assumed to be Concomitant-only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the first dose of study drug. If there is clear evidence to suggest that the medication started prior to the first dose of study drug, the medication will be assumed to be Prior-and-Concomitant, unless there is clear evidence to suggest that the medication stopped prior to the first dose of study drug. If there is clear evidence to suggest that the medication stopped prior to the first dose of study drug, the medication will be assumed to be Prior-only.

The following lists the concomitant medication tables to be displayed:

- Number and percentage with at least 1 Prior-only medication by ATC level 3 and PT
- Number and percentage with at least 1 Prior-and-Concomitant medication by ATC level 3 and PT
- Number and percentage with at least 1 Concomitant-only medication by ATC level 3 and PT

The use of concomitant medications will be included in a by-participant data listing.

4.5 PK and ADA Evaluation

The PK analyses will be based on the PK population, unless otherwise specified. TSR-033 and TSR-042 concentration-time data from each arm of the study will be analyzed using standard non-compartmental methods. Combined PK data from this study and other studies may also be analyzed in a population PK approach using nonlinear mixed effects modeling and the results of which, if performed, may be reported separately.

4.5.1 *Pharmacokinetic Analyses*

4.5.1.1 Endpoint / Variables

Drug Concentration Measures

Blood sampling time will be related to the start of dosing. Serum concentrations will be listed and summarized by cohort, dose and nominal time.

Derived Pharmacokinetic Parameters

TSR-033 and TSR-042 PK parameters will be calculated by standard non-compartmental analysis according to current working practices and using Phoenix.

All calculations of non-compartmental PK parameters will be based on actual sampling times. For each participant and for each dose, PK parameters described in Table 8 will be determined from the TSR-033 and TSR-042 serum concentration-time data and additional parameters may be explored as data permit.

All PK parameters will be listed and summarized descriptively by cohort and dose. Summary statistics will include mean, standard deviation, coefficient of variation (CV), geometric mean, geometric mean CV, median, minimum, and maximum.

Table 8 Derived Pharmacokinetic Parameters

Parameter	State	Parameter Description
AUC(0-last)	sd, md	Area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-∞)*	sd, md	Area under the serum concentration-time curve from time zero extrapolated to infinity will be calculated as, if data permit: AUC(0-∞) = AUC(0-t) + C(t) / lambda_z
AUCtau	md	Area under the serum concentration-time curve during the dosing interval using the linear/log trapezoidal rule; AUC0-336 - Area under the serum concentration-time curve from time zero to 336 hours; AUC0-504 - Area under the serum concentration-time curve from time zero to 504 hours
Cmax	sd, md	Maximum observed serum concentration, determined directly from the serum concentration-time data.
Cmin	sd, md	Minimum observed serum concentration, determined directly from the serum concentration-time data.
tmax	sd, md	Time to reach Cmax, determined directly from the serum concentration-time data.
Lambda_z	sd, md	Apparent terminal phase elimination rate constant. The lambda_z lower and upper limits and number of points used to determine lambda_z will also be reported.
t½*	sd, md	Apparent terminal phase half-life will be calculated as: t½ = ln2 / lambda_z (terminal phase elimination rate constant)
CL	sd, md	Clearance. CL=dose / AUC(0-∞) for sd
Vz	sd, md	Volume of distribution. For non-steady-state data: Vd=dose/ (λz x AUC(0-∞)) for sd; Vd=dose/(λz x AUCtau) for md
Vss	md	Volume of distribution at steady state, calculated from: Vss = CL x MRT (mean residence time), if data permit.
AR(cmax)	md	Accumulation ratio based on Cmax.
AR(AUC)	md	Accumulation ratio based on AUC.

- sd: single dose; md: multiple dose
- *: if data permit
- Additional parameters may be included as required.

4.5.1.2 Strategy for Intercurrent (Post-Randomization) Events

Missing concentrations and concentrations below the limit of quantification of the assay will be handled as described in Guidance Document VQD-GUI-000722.

Drug concentration data which are below the lower limit of quantification, LLQ (70.0 ng/mL for TSR-033 and 32.0 ng/mL for TSR-042) will be imputed to zero.

Concentrations that are inconsistent pharmacokinetically with the drug concentration-time profile within an individual may be considered as outliers and subsequently excluded from the dataset or analysis. Visual inspection of individual and pooled data and weighted residuals during analysis may be used to identify such outliers. Any such exclusion will be reported and discussed in the final report.

Missing data will be handled in the following way:

- Participants who withdrew from the study and did not provide any PK samples and do not have adequate sampling and/or covariate information will be excluded from the analysis

- If dosing and/or sampling times are missing, the relevant concentrations may be excluded from the analysis dataset and summarized in an exclusion listing file. Alternatively, the nominal times of the respective doses and/or samples may be utilized

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4.5.3 Immunogenicity Analyses

The immunogenicity of anti-TSR-033 antibodies antibodies will be summarized and listed. Immunogenicity will be based on the Immunogenicity (ADA) population.

The ADA sample results for the samples at each available timepoint, including pre-dose and post-dose will be categorized into different ADA sample status: ADA-positive samples, ADA-negative samples, and ADA-inconclusive samples. ADA-positive sample is identified when ADA is detected (ADA response is above the cut point in the confirmatory assay). ADA-negative sample is identified when ADA is not detected (ADA response is below the cut point in the screening assay, or above the cut point in the screening assay but below the cut point in the confirmatory assay). ADA-inconclusive sample is identified when ADA is not detected in a sample, but the drug is present in the sample at a level higher than the drug tolerance for the ADA assay. Unevaluable samples which could not be tested for ADA status due to inadequate sample volume, mishandling, or errors in sample collection, processing, storage, etc. will not have any ADA data and thus no results will be reported.

The number and percent of participants who become positive for ADAs and who develop neutralizing antibodies will be summarized by dose regimen, part, visit/time and overall.

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4.7 Additional Analyses Due to the COVID-19 Pandemic

The definition of the phases of the COVID-19 pandemic measures is given in Appendix 7.2

COVID-19 cases will be captured on the COVID-19 Coronavirus Infection Diagnosis and Assessment CRF pages based on the WHO criteria using the categories of: suspected, probable, and confirmed cases. The COVID-19 infected subpopulation will be summarized in a table including the number of subjects with suspected, probable, or confirmed COVID-19 diagnosis, the number of subjects with suspected, probable, or confirmed worst case COVID-19 case diagnosis, the number of subjects with suspected, probably, or confirmed COVID-19 Case Diagnosis Events, the number of subjects who had a COVID-19 test performed, and the number of subjects with positive, negative, or indeterminate COVID-19 test results.

A summary of the number of participants recruited by country and site relative to the COVID-19 pandemic measures may be provided. A figure of the number of participants recruited over time by country relative to the COVID-19 pandemic measures may also be presented.

A listing of the start dates of COVID-19 pandemic measures overall and by country may be listed.

5 CHANGES TO PLANNED ANALYSES

In the protocol, the Per Protocol Population is defined as, “All participants in the Efficacy Population who do not have protocol violations during the study that may significantly impact the interpretation of efficacy results and have ≥1 post-baseline disease assessment”. This definition is changed in the SAP to, “All participants in the Efficacy Population who have no major (i.e. important) protocol violations during the study and have ≥1 post-baseline disease assessment”. The original language in the protocol was as per the TESARO PDMS, and this language was updated in the SAP to align with GSK PDMS.

6 REFERENCES

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7 APPENDIX

7.1 Immune-related Adverse Events

A list of MedDRA PTs and system organ class (SOC) that will be used to identify immune-related adverse events will be shared with the programming team separately for reference.

7.2 Definition of when COVID-19 Pandemic Measures Began

Pandemic measures began in different countries at different times. A dataset containing the date when pandemic measures began, as determined by the GSK country Issue Management Teams (IMT), will be used to determine the start date of pandemic measures within each country. A copy of this dataset will be taken at the time of database freeze (DBF).

The alert levels are escalated and de-escalated over time and the scale used for the recording of alerts is standardized: green (low impact), yellow (low to moderate impact), orange (moderate to high impact), red (high impact), and black (high impact with severe disruption). Date of when pandemic measures began was defined based on the IMT alert levels and used in analyses.

Adverse events will be summarizing according to whether the onset date was before, during or after the start of the COVID-19 pandemic measures.

The initial start date is being defined as when the COVID-19 IMT alerts for each country were all initially activated with an alert level of Yellow or above. The end date of this first wave will be defined as when the alert level has de-escalated to green.

Pandemic Measures Phase	Definition
Pre	AE onset date < pandemic measures start date
During	Pandemic measures start date ≤ AE onset date < pandemic measures end date
Post	AE onset date ≥ pandemic measures end date

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